Preoperative inflammatory mediators and postoperative delirium: systematic review and meta-analysis

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Abstract

Background: Postoperative delirium has eluded attempts to define its complex aetiology and describe specific risk factors. The role of neuroinflammation as a risk factor, determined by measuring blood levels of preoperative ‘innate’ inflammatory mediator levels, has been investigated. However, results have been conflicting. We conducted a systematic review and meta-analysis of the evidence on associations between preoperative blood levels of inflammatory mediators and postoperative delirium in the older person. Influence of type of surgery was also assessed.

Methods: Original, low risk of bias studies, published in peer-reviewed journals, which fulfilled the eligibility criteria were included. Seventeen articles fulfilled study criteria. Data extraction, synthesis, and risk of bias analysis were guided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and quality in prognostic studies guidelines. Meta-analyses used a random-effects model. Inflammatory mediators included C-reactive protein, interleukin-6, -8, and -10, tumour necrosis factor-α, insulin-like growth factor-1, cortisol, and neopterin. Surgical groups were cardiac, noncardiac, and hip fracture.

Results: Higher preoperative interleukin-6 was associated with postoperative delirium with a standardised mean difference (95% confidence interval) of 0.33 (0.11–0.56) and \( P=0.003 \). Higher neopterin was also associated with postoperative delirium.

Conclusions: The association of preoperative blood levels of inflammatory mediators with postoperative delirium may be influenced by the type of surgery and the specific mediator. The potential modulating effect of type of surgery, intrinsic brain vulnerability, and the complex interactions between inflammatory mediators and binding proteins will need to be considered in future studies.

Clinical trial registration: CRD42019159471 (PROSPERO).

Keywords: cytokines; delirium; inflammatory markers; neuroinflammation; older people; postoperative delirium

Editor’s key points

- Systemic inflammation is thought to be a driver for postoperative delirium, usually as a result of the surgery. It is less clear whether preoperative inflammatory responses to the injury and its sequelae are associated with delirium.

- This review highlights a clear association between preoperative interleukin-6 concentrations and postoperative delirium, but the evidence for other inflammatory markers is less clear.

- There is marked heterogeneity of timing of cytokine measurement and the assessment of delirium which hinders assessment, and there is a need for a
Postoperative delirium (POD) in older people is increasingly recognised as a complication of surgery that has significant short- and long-term consequences for the cognitive and functional integrity of the individual patient. Although the aetiology of POD is as yet unclear, some proposed mechanisms are neuroinflammation, neurotransmitter imbalance, network dysconnectivity, cortisol excess, and genetics. These may contribute in isolation, or in combination, to the pathophysiology of POD.

Exploration of the role of neuroinflammation in the aetiology of POD is made complex by blood–brain barrier integrity and permeability, immunoosenescence, intracranial production of cytokines, peripherally produced cytokines, and yet-to-be-discovered inflammatory mediators. Also, it is important to differentiate between risk markers, that is inflammatory mediator levels innate to the individual patient before the onset of the anaesthesia-surgical intervention, and disease markers that occur during the episode of POD.

Despite these challenges, an exploration of neuro-inflammation as a mechanistic aetiological factor for POD is attractive. An association between neuroinflammation and dementia, a ‘chronic cognitive impairment’, has already been demonstrated; thus, the notion that neuroinflammation may contribute to POD, an ‘acute cognitive impairment’, is conceivable.

More proximal measurement of brain inflammatory mediators (i.e. cerebrospinal fluid levels) may provide some clarity on the role of neuroinflammation in POD, but this is ethically and practically problematic in people who do not require spinal anaesthesia. An oft used surrogate is the measurement of blood levels of inflammatory mediators with the caveat that these represent only those substances that are present in measureable levels in blood. That said, the measurement of blood levels of inflammatory mediators to investigate the aetiology of POD also raises the possibility of its use as a risk marker of POD. In addition, an association between preoperative inflammatory markers and POD may have relevance to other settings of delirium, particularly acute medical illness. In those settings, almost invariably assessments can be made only once an inflammatory insult has potentially occurred. The surgical setting provides an opportunity to assess inflammatory state when acute illness is largely absent – with the obvious exception of hip fracture.

Investigators of biomarkers of POD have explored either individual or panels of inflammatory mediators, with conflicting results. Frequently investigated potential risk markers have included C-reactive protein (CRP) and interleukin-6 (IL-6). The roles of neopterin, insulin-like growth factor-1 (IGF-1), and cortisol in POD have also been explored albeit to a lesser extent.

**Objectives**

This review aims to synthesise the evidence for blood levels of inflammatory mediators as risk markers of POD in older people (age 65 yr and above).

**Methods**

Protocol and registration: PROSPERO (Registration ID CRD42019159471) ([https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019159471](https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019159471)).

This review is part of work funded by a British Journal of Anaesthesia/Royal College of Anaesthetists (BJA/RCoA) Project Grant. The report has been structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

**Eligibility criteria**

The main eligibility criteria were: mean age ≥65 yr in the POD group, inflammatory mediator levels sampled preoperatively, stated timing of preoperative blood sample, exclusion of preoperative delirium or identification of subgroup without preoperative delirium, clearly stated method of assessment of POD, and comparison of inflammatory mediator levels between POD group and no delirium group. Original studies published in peer-reviewed journals were included; review articles, letters, and duplicate reports were excluded.

**Information sources**

**Published reviews**

A search was conducted for existing systematic reviews on inflammatory mediators as risk markers for POD. Databases searched included the Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR), PubMed reviews, Medline reviews, Joanna Briggs Institute (JBI) database of systematic reviews and implementation report, and PROSPERO international prospective register of systematic reviews. Details of the search strategy used are in Supplementary Appendix 1. From the search results, we identified three reviews that are relevant to our current review. A comprehensive review by Liu and colleagues examined inflammatory markers in POD and postoperative cognitive impairment. Our review will include only studies judged to be of low risk of bias. Currently available studies also allowed us to assess hip fracture surgery studies as a subgroup. Activation of the inflammatory cascade caused by the trauma and subsequent hip fracture predates admission and preoperative blood sampling, making hip fracture surgery participants a distinct subgroup. In view of the effect of cardiopulmonary bypass, as in the study of Liu and colleagues, articles on cardiac surgery patients were analysed separately. Another review was limited to articles published between January 2016 and June 2018. Finally, the review by Ayob and colleagues examined preoperative biomarkers and imaging as predictors of POD in noncardiac surgery. It is a comprehensive qualitative review, but the limited number of available articles precluded quantitative analysis.

**Current review**

A search of Medline, PubMed, Embase, Scopus, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Cochrane Library, Web of Science, and PsycInfo was conducted by two independent researchers (AN and DA) to identify articles relevant to this review. Databases were searched for articles up to January 15, 2021 with subsequent surveillance using alert systems. The references of identified articles...
and systematic reviews were also searched for further relevant articles.

**Search**

Our search strategy included terms for POD and inflammatory mediators. Details of our search strategy are included in Supplementary Appendix 1.

**Study selection**

Study selection process is depicted in the flowchart (Supplementary Appendix 2).

**Data collection process**

Data collection was performed, using a piloted form, by two researchers (AN and DA).

**Data items**

Data items collected included article characteristics, participant characteristics, delirium assessments, blood processing, inflammatory mediators assayed preoperatively, values of markers (if provided), result of statistical analysis, and differences in confounders between groups.

A detailed list of data items is included in Supplementary Appendix 1.

**Risk of bias in individual studies**

The quality in prognostic studies (QUIPS) tool was used to assess the risk of bias of articles included in this review. The six domains assessed were study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Risk of bias was assessed independently by three researchers (AN, DA, and RE) (Supplementary Appendix 3).

This review is a synthesis of studies that were judged as having low risk of bias. Factors that contributed to our judgement of high risk of bias included convenience sampling of participants, high post-recruitment drop-out rate, unstated interval between preoperative blood sampling and surgery, inflammatory mediator assay method not clearly described, screening for preoperative delirium not stated, and retrospective assessment for determining incidence of POD.

**Summary measures**

Standardised mean difference of preoperative inflammatory mediator levels.

**Risk of bias across studies**

For each inflammatory mediator, risk of publication bias across studies was assessed using visual inspection of funnel plots. However, the number of articles available for each inflammatory mediator did not reach the threshold for meaningful assessment of publication bias (Supplementary Appendix 4).

**Synthesis of results and additional analysis**

A narrative summary for each inflammatory mediator was performed on all studies that met the review criteria to facilitate inclusion of high-quality studies that did not specify the values of measured mediators. Quantitative analysis for each inflammatory mediator was performed where data were available. Subgroups for each inflammatory mediator were determined based on type of surgery (i.e. cardiac surgery, hip fracture surgery, and noncardiac surgery), and categories were elective, emergency, or mixed. Mixed refers to studies in which the elective and emergency participants were not separated in the study or the urgency was unstated. Additional meta-analysis was performed on studies or subgroups that excluded patients with dementia. Meta-analysis was performed using Review Manager 5.3 (RevMan 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and R platform (version 3.5.2 using the Meta package, R Foundation for Statistical Computing, Vienna, Austria). A random-effects model was used. The measure of effect size was standardised mean difference ($\delta$) and the confidence interval (CI) was 95%. Higgins’ $I^2$ was used to assess heterogeneity. Data expressed in median (inter-quartile range [IQR]) were converted to mean (standard deviation [SD]) using the method described by Luo and colleagues and Wan and colleagues. Mediator levels presented as mean (standard error of mean) were converted to mean ($\mu$).

**Results**

**Study selection**

Our search yielded 9519 articles from which 17 low risk of bias articles relevant to our review were identified after removal of duplicates, non-relevant articles, and review articles (Supplementary Appendix 2).

Across studies, the median (IQR) incidence of POD was 24% (21–32%).

**Study characteristics**

Characteristics of included studies are shown in Table 1.

**Risk of bias within studies**

Details of our risk of bias analysis are depicted in Supplementary Appendix 3.

**C-reactive protein**

**General**

Nine original studies explored the association between preoperative CRP and POD. Two further articles were excluded because they contained participants included in one of the aforementioned studies. The majority were prospective cohort studies (of which consecutive recruitment was used in six studies) and case–control design was used in three studies.

**Delirium assessment**

A variety of tools were used to assess POD; however, all were under the umbrella of the Diagnostic and Statistical Manual (DSM) of mental disorders’ criteria for delirium. These included the confusion assessment method (CAM), delirium rating scale (DRS), and a combination of DRS and CAM. Delirium assessments were performed by a psychiatrist, a psychiatrist or another person in two studies (geriatrician, trained researcher) and trained study staff adjudicated by delirium experts, a trained researcher confirmed by a psychiatrist, trained assessors, an expert in...
psychology, an anaesthesiologist, and a clinical team. Delirium assessments were performed twice daily for a variable number of days in four and daily, also for a variable number of days.

**CRP measurement**

The duration between preoperative blood sampling and surgery was variable. Blood sampling occurred on the day before surgery in five studies, before surgery via a femoral catheter, within 12 h after admission, preoperative (likely within the 24 h before surgery), and at the pre-admitting testing centre (average, 2 weeks before surgery).

**Qualitative analysis**

Raised preoperative CRP was associated with subsequent POD in five of the nine studies. This association remained on multivariate analysis in two studies.

**Meta-analysis**

A quantitative analysis was performed on six studies that had data available. These included 402 participants with POD and 1589 participants without POD. There was no significant difference in preoperative CRP between people who subsequently developed POD compared with those who did not. The SMD was 0.42 (95% CI, −0.19 to 1.04; P = 0.18). However, there was significant heterogeneity in the included studies (Higgins’ I² = 96%). Subgroup analysis included two studies on cardiac surgery, two on hip fracture surgery, and two on noncardiac surgery (elective and mixed). The cardiac surgery subgroup included 187 participants with POD and 906 participants without. The SMD was 0.26 (95% CI, 0.09 to 0.42; P = 0.002). Higgins’ I² was 0%. In the hip fracture surgery subgroup, there were 161 participants with POD and 529 without. The SMD was 1.02 (95% CI, −0.31 to 2.35; P = 0.13). Higgins’ I² was 97%. Finally, for noncardiac surgery, which

<table>
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<tr>
<th>Table 1 Characteristics of articles included in review</th>
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<tr>
<td><strong>Authors</strong></td>
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<tr>
<td>Osse and colleagues</td>
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<td>Shen and colleagues</td>
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<td>Guo and colleagues</td>
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<td>Slor and colleagues</td>
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<td>Lemstra and colleagues</td>
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<td>Cerejeira and colleagues</td>
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<td>Vasunilashorn and colleagues</td>
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<tr>
<td>Sun and colleagues</td>
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<tr>
<td>Chen and colleagues</td>
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<tr>
<td>Vasunilashorn and colleagues</td>
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<tr>
<td>Liu and colleagues</td>
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<td>Capri and colleagues</td>
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<td>Peng and colleagues</td>
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<tr>
<td>Cerejeira and colleagues</td>
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<td>Chu and colleagues</td>
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<tr>
<td>Kazmierski and colleagues</td>
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<td>Kotfis and colleagues</td>
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CAM, confusion assessment method; DRS, delirium rating scale; CRP, C-reactive protein; IL, interleukin; IGF-1, insulin-like growth factor 1; TNF-α, tumour necrosis factor alpha; POD, postoperative delirium; IQR, inter-quartile range.

* Results for whole cohort from which cases and controls were selected.
included 54 participants with POD and 154 without, the SMD was 0.02 (95% CI, 0.29 to 0.33; \(P = 0.88\)). Higgins’ \(I^2\) for the noncardiac subgroup was 0% (Fig. 1).

Further analysis was conducted which included only studies on participants who did not have preoperative dementia. There were four studies, which included 326 participants with POD and 1472 participants without POD.\(^{17}\) In this analysis, raised preoperative CRP was not associated with POD. The SMD was 0.60 (95% CI, 0.21 to 1.42; \(P = 0.15\)). Higgins’ \(I^2\) was 97% (Fig. 2).

**IL-6 measurement**

Preoperative blood sampling occurred before anaesthesia in two studies,\(^{24,26}\) before surgery via a femoral catheter, \(^{23}\) day before surgery in three,\(^{17,21,28}\) within 12 h of admission,\(^{20}\) morning of admission day,\(^{27}\) and at the pre-admitting centre.\(^{25}\) IL-6 levels were determined using enzyme linked immunosorbent assay (ELISA) in six studies,\(^{17,20,23,24,26,28}\) and various forms of multiplex assays.\(^{21,25,27}\)

**Qualitative analysis**

There was no association between preoperative IL-6 and POD in six studies.\(^{20,21,24,26}\) An association between raised preoperative IL-6 and POD was found in three studies\(^{17,27,28}\) and the association was maintained on multivariate analysis in one study.\(^{27}\)

**Meta-analysis**

Six studies had data on preoperative IL-6 and POD and were included in the meta-analysis.\(^{17,20,24,26}\)

These included 281 participants with POD and 874 participants without. Preoperative IL-6 was significantly higher in participants who developed POD compared with those who

<table>
<thead>
<tr>
<th>Source</th>
<th>CRP cardiac surgery</th>
<th>CRP higher in no delirium</th>
<th>CRP higher in delirium</th>
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<tbody>
<tr>
<td>Osse 2012</td>
<td>0.22 [−0.13; 0.57]</td>
<td></td>
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<tr>
<td>Kofis 2019</td>
<td>0.27 [0.08; 0.45]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.26 [0.09; 0.42]</td>
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</tr>
<tr>
<td>Heterogeneity: (\chi^2_{5}=0.05) ((P=0.82)), (I^2=0%)</td>
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<td>Test for overall effect: (z=3.05) ((P=0.002))</td>
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<tr>
<th>CRP hip fracture surgery</th>
<th>CRP non−cardiac surgery</th>
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</thead>
<tbody>
<tr>
<td>Slor 2019</td>
<td>0.33 [−0.05; 0.71]</td>
</tr>
<tr>
<td>Guo 2016</td>
<td>1.69 [1.46; 1.91]</td>
</tr>
<tr>
<td>Total</td>
<td>1.02 [−0.31; 2.35]</td>
</tr>
<tr>
<td>Heterogeneity: (\chi^2_{5}=36.16) ((P&lt;0.001)), (I^2=97%)</td>
<td>Test for overall effect: (z=1.50) ((P=0.13))</td>
</tr>
<tr>
<td>Total</td>
<td>0.42 [−0.19; 1.04]</td>
</tr>
<tr>
<td>Heterogeneity: (\chi^2_{5}=123.18) ((P&lt;0.001)), (I^2=96%)</td>
<td>Residual heterogeneity: (\chi^2_{5}=36.75) ((P&lt;0.001)), (I^2=92%)</td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: (z=1.35) ((P=0.18))</td>
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</table>

**Fig 1.** Forest plot of preoperative C-reactive protein (CRP) levels and incidence of postoperative delirium. SMD, standardised mean difference; CI, confidence interval.
did not. The SMD was 0.33 (95% CI, 0.11 to 0.56; \(P = 0.003\)). Higgins’ \(I^2\) was 58%.

The number of studies included in each subgroup was three for elective noncardiac,17,26,28 two for mixed noncardiac,20,27 and one for cardiac surgery.24 Preoperative IL-6 was higher in participants with POD in the mixed noncardiac surgery subgroup (SMD = 0.73; 95% CI, 0.33–1.13; \(P = 0.0004\); Higgins’ \(I^2\) = 18%). No significant difference was found in cardiac surgery and elective noncardiac (\(P = 0.05\) and 0.16, respectively) (Fig. 3).

Four studies of the studies had data on participants who did not have preoperative dementia.17,26,28 These included 178 participants with POD and 643 participants without delirium. Preoperative IL-6 was associated with the incidence of POD in this analysis. The SMD was 0.26 (95% CI, 0.01–0.51; \(P = 0.04\)). Higgins’ \(I^2\) was 51% (Fig. 4).

### IL-8 and IL-10

**General**

Three studies assessed the association between preoperative IL-8 and IL-10, and POD.21,25,27 Study design was case-control in two25,27 and consecutive cohort recruitment.21 Surgical specialties were elective noncardiac21,25 and mixed noncardiac.27

**Delirium assessment**

CAM was used in all studies. Delirium assessments were performed by trained researchers,27 a psychiatrist,21 and trained researchers adjudicated by delirium expert.25 Assessments were performed daily for a variable number of days in all studies with one study specifying once daily.21

### IL-8 and IL-10 measurement

Preoperative blood sampling occurred on the day before surgery,21 morning of hospital admission,27 and at the pre-admitting testing centre.25 IL-8 and IL-10 were measured using multiplex assay in all studies.

**Qualitative analysis**

There was no association between preoperative IL-8/IL-10 and POD in any of the studies. The study by Vasunilashorn and colleagues25 found an association between POD and raised preoperative IL-8 in their discovery cohort, but this was not maintained when assessed in the pooled (larger) cohort.

**Meta-analysis**

Only one study presented values for cytokines; thus a meta-analysis was not conducted.

### Tumour necrosis factor-alpha

**General**

There were three studies investigating an association between preoperative tumour necrosis factor-alpha (TNF-\(\alpha\)) and POD.21,25,28 Study design was consecutive cohort in two21,28 and case-control.25

**Delirium assessment**

CAM was used in two studies,21,25 and DSM-V criteria by a psychiatrist.28 Delirium assessment was performed by
psychiatrists in two\cite{Peng2019,Shen2016} and trained researchers\cite{Liu2013}. Delirium assessments were performed daily, for a variable number of days, in all studies.

### TNF-α measurement

Preoperative blood sampling occurred on the day before surgery in two studies\cite{Peng2019,Shen2016}, and at the pre-admitting testing centre\cite{Liu2013}. ELISA was used in one study\cite{Shen2016} and multiplex assay was used in the others.

### Qualitative analysis

Preoperative TNF-α was significantly higher in the POD group in one study\cite{Liu2013}, but this significance was lost on multivariate analysis\cite{Peng2019}.

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**Fig 3.** Forest plot of preoperative interleukin-6 (IL-6) levels and incidence of postoperative delirium. SMD, standardised mean difference; CI, confidence interval.

**Fig 4.** Forest plot of preoperative interleukin-6 (IL-6) levels in people without preoperative dementia and incidence of postoperative delirium. SMD, standardised mean difference; CI, confidence interval.
Meta-analysis

Only one study,28 presented data for TNF-α, so a meta-analysis was not conducted.

Insulin-like growth factor 1

General

Four studies explored the association between preoperative IGF-1 and POD.17,20,29,30 All studies were prospective and one was case-control design.20 Surgical specialties were mixed noncardiac surgery in two,20,30 and elective noncardiac surgery.17,29

Delirium assessment

Delirium assessment utilised CAM in three studies, and DRS and CAM.17 Delirium assessments were performed by trained researcher confirmed by a psychiatrist in two,17,30 trained researchers,20 and a psychiatrist.29 Assessments were performed daily in three studies and twice daily in one.17

IGF-1 measurement

Preoperative blood sampling was on the day before surgery in three studies,17,29,30 and within 12 h of admission.29 ELISA was used in all studies.

Qualitative analysis

Preoperative IGF-1 was significantly lower in the POD group in one study, and this was sustained on multivariate analysis.17 Three studies did not find an association between preoperative IGF-1 levels and subsequent POD.

Cortisol

General

There were three studies on preoperative cortisol levels and POD.23,29,31 Two studies were on elective noncardiac surgery23,29 and one on elective cardiac surgery.31 Study designs were consecutive cohort in two29,31 and case-control.23

Delirium assessment

CAM was used in two studies23,29 and CAM-ICU in one.31 Delirium assessments were performed by psychiatrists in two studies29,31 and an expert in psychology.23 Delirium assessments were performed twice daily in two studies23,31 and daily.29

Cortisol measurement

Preoperative blood sampling occurred on the day before surgery between 08:00 and 09:00,17 morning of the day before surgery,29 and before surgery.23 Cortisol assay methods

<table>
<thead>
<tr>
<th>Source</th>
<th>SMD (95% CI)</th>
<th>IGF-1 less in delirium</th>
<th>IGF-1 less in no delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chu 2016</td>
<td>0.02 [-0.44; 0.48]</td>
<td></td>
<td></td>
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<tr>
<td>Lemstra 2008</td>
<td>0.38 [-0.16; 0.92]</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.17 [-0.18; 0.52]</td>
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<tr>
<td>Heterogeneity: $\chi^2=0.99$ ($P=0.32$), $I^2=0%$</td>
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<tr>
<td>Test for overall effect: $z=0.96$ ($P=0.34$)</td>
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<table>
<thead>
<tr>
<th>Source</th>
<th>SMD (95% CI)</th>
<th>IGF-1 less in delirium</th>
<th>IGF-1 less in no delirium</th>
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<tbody>
<tr>
<td>Shen 2016</td>
<td>−0.08 [-0.45; 0.30]</td>
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<tr>
<td>Cerejeira 2013</td>
<td>0.17 [-0.24; 0.57]</td>
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<tr>
<td>Total</td>
<td>0.04 [-0.24; 0.32]</td>
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<tr>
<td>Heterogeneity: $\chi^2=0.75$ ($P=0.39$), $I^2=0%$</td>
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<tr>
<td>Test for overall effect: $z=0.27$ ($P=0.79$)</td>
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<tr>
<th>Source</th>
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<tr>
<td>Cerejeira 2013</td>
<td>−0.08 [-0.45; 0.30]</td>
<td></td>
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</tr>
<tr>
<td>Total</td>
<td>0.17 [-0.16; 0.92]</td>
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<tr>
<td>Heterogeneity: $\chi^2=2.08$ ($P=0.56$), $I^2=0%$</td>
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<tr>
<td>Residual heterogeneity: $\chi^2=1.74$ ($P=0.42$), $I^2=0%$</td>
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<tr>
<td>Test for overall effect: $z=0.80$ ($P=0.42$)</td>
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Fig 5. Forest plot of preoperative insulin-like growth factor 1 (IGF-1) levels and the incidence of postoperative delirium. SMD, standardised mean difference; CI, confidence interval.

Meta-analysis

All four studies had sufficient data for inclusion in meta-analysis. Data expressed as nmol L⁻¹ were converted to ng ml⁻¹.

The studies included 114 participants who developed POD and 298 who did not. Preoperative IGF-1 was not associated with the incidence of POD (SMD=0.09; 95% CI, −0.13 to 0.31; P=0.42). Higgins’ $I^2$ was 0%. Analysis including only studies on elective noncardiac surgery participants (two studies)17,29 yielded similar results (SMD=0.04; 95% CI, −0.24 to 0.32; P=0.79) (Fig. 5).
Preoperative neopterin levels may also be associated with POD in cardiac surgery patients. An association was found and confirmed on adjusted analysis in one study. Our results suggest reasonable evidence for an association between preoperative, IL-6 and POD. Higher preoperative CRP did not. This persisted after adjustment for confounders.

**Qualitative analysis**

No association was found between preoperative cortisol levels and POD in two studies. An association was found and confirmed on adjusted analysis in one study.

**Meta-analysis**

Two studies had data to include in a quantitative analysis. There were 78 patients who had POD and 136 without delirium. There was no significant association between preoperative cortisol and POD. The SMD was 0.16 (95% CI, –0.68 to 1.00; P=0.71; Higgins' $I^2=89\%$) (Supplementary Appendix 5).

**Neopterin**

**General**

Although we identified three studies exploring the association between preoperative neopterin levels and POD, only one fulfilled the low risk of bias requirement for this review. It was a prospective cohort study on elective cardiac surgery patients.

**Delirium assessment**

CAM-ICU was used by an investigator or a psychiatrist to assess POD. Delirium assessments were performed daily.

**Neopterin measurement**

Preoperative blood sampling occurred on the day before surgery and was measured using high-performance liquid chromatography.

**Qualitative analysis**

Preoperative neopterin was significantly higher in participants who subsequently developed POD compared with those who did not. This persisted after adjustment for confounders.

**Discussion**

Our results suggest reasonable evidence for an association between preoperative, IL-6 and POD. Higher preoperative CRP may be associated with POD in cardiac surgery patients. Preoperative neopterin levels may also be associated with POD but more, high-quality, studies are required to validate this. There is reasonable evidence for a lack of association between preoperative levels of IL-8, IL-10, TNF-α, and IGF-1, and the incidence of POD. Preoperative cortisol level was not associated with the incidence of POD. However, given the variety of blood sampling times, and in light of the diurnal variation of cortisol levels, the accuracy of this finding is unclear.

Despite extensive review of the literature, considerable uncertainty remains about the significance of blood levels of inflammatory mediators and the incidence of subsequent POD in older people. Some of the uncertainty is attributable to differences in study design, timing of delirium assessments and of blood samples, methods of inflammatory mediator assay, recruitment patterns, and variable handling of dementia. That said, the concept that inflammatory mediators may play a role in the pathogenesis of POD and could be used to identify the risk of POD in older people, has some merit. It is important to acknowledge that peripheral cytokine levels may not accurately reflect cerebral cytokine levels and by extension, neuroinflammation. There are some studies that have investigated closer, although still not direct, measures of neuroinflammation, using CSF sampling. However, these studies are generally only possible in those having spinal anaesthesia, which may introduce an element of selection bias.

Thus far, investigation of the role of inflammatory mediators in POD has largely focused on either a mediator in isolation or a group of mediators. This approach may be too simplistic given the multiplicity of interactions between inflammatory mediators and the complexity of POD. Interactions between inflammatory mediators may include potentiation, induction of secretion, inhibition, or both. Some investigators have tried to accommodate this by using an ‘inflammatory score’, for example pro-inflammatory/anti-inflammatory ratio. Although the idea of an ‘inflammatory score’ may provide some answers, such a score, in the opinion of the authors of this review, brings its own problems. Composite scores implicitly or explicitly incorporate a weighting of the individual factors – the evidence supporting this is not clear. Contributing to this stew of complexity is the dual role of some inflammatory mediators; for example IL-6, widely accepted as a pro-inflammatory mediator, also has anti-inflammatory properties. Carrier proteins of inflammatory mediators are a further confounder. Serum levels of these binding proteins may affect the amount of free, unbound mediators available to influence inflammation (e.g. IGF-1 and IGF binding protein-3).

The potential contribution of the special circumstances associated with certain types of operation to the aetiology of POD must not be overlooked. In particular, cardiac surgery facilitated by cardiopulmonary bypass has associated with it cytokine activation by the bypass circuit and the impact of laminar flow and microemboli on the brain. Hip fracture surgery also presents several challenges as the trauma may already have initiated the inflammatory cascade, rendering inflammatory mediators measured on admission a false assessment of true baseline inflammatory status. It may well be that, in these special cases, it is the increase in inflammatory mediators induced by the anaesthesia-surgical intervention that informs the risk of POD.

Our findings should be interpreted in the context of previous studies that delirium is associated with inflammatory cytokines. We explicitly sought evidence of whether a pro-inflammatory state might increase the risk of developing delirium after surgery. On the basis of the data, we are unable to conclude whether people with higher inflammatory markers had early (not clinically detected) delirium, or whether they truly developed delirium de novo in the postoperative period. There is also some evidence that frailty, which is itself associated with POD, is a state of chronic low-grade inflammation. Either way, it is plausible, that appropriate modulation of this inflammatory response might reduce POD risk. Formal trials of putative therapeutic interventions will be necessary.

Finally, evidence of unique vulnerability of the brain of certain patients has been described. The interplay between cytokine surge and innate brain vulnerability is fertile ground for future exploration.
There are limitations to our review. Assessment of peripheral inflammatory markers in the aetiology of a complex and multifaceted phenotype, POD, although useful, may be a simplistic approach. Unravelling the aetiology of POD requires a deep exploration of multiple influences on the levels, interactions, and activity of inflammatory markers in the context of surgical type and intrinsic vulnerability (frailty, neural, or both) of patients. In addition, the variability in methodology of currently available studies limits the availability of high-quality, congruent studies from which strong evidence can be synthesised. As is common with systematic reviews, we included studies where POD was a clearly identifiable outcome, even if it was not the single primary outcome. This increases the number of studies but may risk increased heterogeneity and issues with data quality. We suggest that future researchers in this field should consider certain methodological factors such as timing of preoperative blood tests, frequency of delirium assessments, careful screening for preoperative delirium, and accurate accounting for confounders. There may be a role for experts in the field to formally publish recommendations for a minimal dataset for future research as has become common with clinical trials. This might usefully encompass minimum requirements for POD diagnosis, timing of assessments, and characterisation of surgical and perioperative care.

On the basis of our review, we would suggest that such an approach would include: formal, prospective assessment of delirium using a validated tool on more than one occasion; at least one paired before and after blood sample, preferably with at least two postoperative samples at mediator-specific times to capture the likely peak and time-course of mediators; IL-6 as an active control to demonstrate likely comparability between study groups. Ideally, analysis should allow exploration of interactions and the impact of other mediating mechanisms such as protein binding and receptor concentrations. There are theoretically at least three different surgical cohorts that merit exploration separately: cardiac surgery; elective noncardiac surgery; and surgery after an inflammatory insult (injury, intra-abdominal pathology). Although POD can occur at any age and after a variety of surgical interventions, there may be benefit in researchers using delirium risk tools to maximise returns on research investment.

‘Future research into the role of preoperative inflammatory mediators in the aetiology of POD, and as a risk marker of POD, may be strengthened by having a standardised approach and incorporating a measure of the individual brain’s unique vulnerability.

Authors’ contributions
Concept: IKM, AN.
Literature search and data collection: AN, DA.
Risk of bias analysis: AN, DA, RE.
Data analysis: IKM, AN.
Images: IKM, AN.
Manuscript: AN (writing and review), DA (review), RE (review), IKM (writing and review).

Acknowledgements
We express our sincere gratitude to Jennie Spendlove, technical support, for her thorough review of, and advice on this manuscript.

Declarations of interest
The authors declare that they have no conflicts of interest.

Funding
British Journal of Anaesthesia and the Royal College of Anaesthetists (to A.M. Noah).

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.04.033.

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Handling editor: Jonathan Hardman